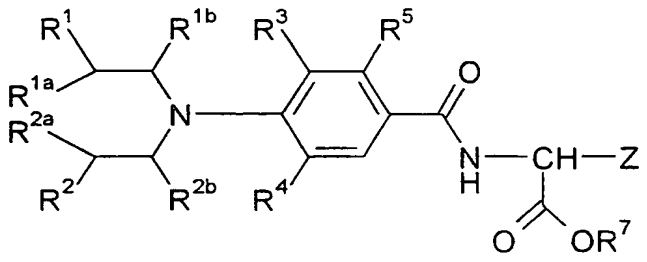
CLAIMS

1. A compound of Formula I:



wherein:

R^1 is -Cl, -Br, -I, $-OSO_2CH_3$, or $-OSO_2Ph$;
R^2 is -Cl, -Br, -I, $-OSO_2CH_3$, or $-OSO_2Ph$;
wherein Ph denotes a phenyl group which is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from a C_{1-4} alkyl group, -F, -Cl, -Br, -I, -CN, or $-NO_2$;

R^{1a} is -H, a C_{1-4}alkyl group, or a C_{1-4}haloalkyl group ;
R^{2a} is -H, a C_{1-4}alkyl group, or a C_{1-4}haloalkyl group ;
R^{1b} is -H, a C_{1-4}alkyl group, or a C_{1-4}haloalkyl group ;
R^{2b} is -H, a C_{1-4}alkyl group, or a C_{1-4}haloalkyl group ;

R^3 is -F, -Cl, -Br, -I, $-OCHF_2$, -C≡CH, $-OCF_3$, $-CH_3$, $-CF_3$, $-SF_5$, $-SCF_3$, or $-CF_2CF_3$;

R^4 is -H, -F, -Cl, -Br, -I, $-OCHF_2$, -C≡CH, $-OCF_3$, $-CH_3$, $-CF_3$, $-SF_5$, $-SCF_3$, or $-CF_2CF_3$;

R^5 is -H or -F;

with the proviso that if R^4 is -H, then R^3 is not -F;

R^7 is -H, $-C(CH_3)_3$, or $-CH_2-CH=CH_2$;

Z is $-CH_2-T-W$;

T is $-CH_2-$, $-O-$, $-S-$, $-(S=O)-$, or $-(SO_2)-$;

the group $-CH_2-T-$ may optionally be substituted with 1 or 2 substituents, denoted Q^1 and Q^2 respectively, on carbon, wherein Q^1 and Q^2 are independently a C_{1-4}alkyl group or a halogen; or, when Q^1 and Q^2 are bonded to adjacent carbon atoms, Q^1 and Q^2 together may form a C_{3-4}alkylene radical optionally substituted with 1, 2, 3 or 4 substituents independently selected from C_{1-4}alkyl groups and halogens;

W is one of:

(1) $-COOH$;

(2) $-(C=O)OR^8$;

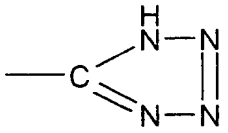
(3) $-(C=O)NR^9R^9$;

(4) $-SO_2NHR^{10}$;

(5) $-SO_2OR^{11}$;

(6) $-PO_3R^{11}R^{11}$;

(7) a tetrazol-5-yl group:



(8) $-CONH-SO_2R^{12}$; and,

(9) -M-Het;

with the proviso that if T is -O-, -S-, -(S=O)-, or $-(SO_2)-$, then W is not -COOH;

wherein:

R^8 is a C_{1-6}alkyl group, a C_{3-6}cycloalkyl group, a C_{5-20}aryl group, or $-CH_2-CH=CH_2$;

wherein the C_{5-20}aryl group may optionally be substituted on carbon with from 1 to 4 substituents

selected from -COOH, -OH, $-NH_2$, $-CH_2NH_2$, $-(CH_2)_{1-4}COOH$, tetrazol-5-yl, and $-SO_3H$;

R^9 is independently -H, a C_{1-6}alkyl group, a C_{3-6}cycloalkyl group, a C_{5-20}aryl group, a C_{7-9}aralkyl group, or a C_{5-20}heteroaryl group linked to N via carbon;

wherein the C_{5-20}aryl group, the C_{5-20}heteroaryl group, and aryl moiety of the C_{7-9}aralkyl group may optionally be substituted on carbon with from 1 to 4 substituents selected from -COOH, -OH, $-NH_2$, $-CH_2NH_2$, $-(CH_2)_{1-4}COOH$, tetrazol-5-yl, and $-SO_3H$;

and wherein the C_{3-6}cycloalkyl group may optionally carry a methyl group;

R^{10} is a C_{1-6}alkyl group, $-CH_2-CH=CH_2$, a C_{3-6}cycloalkyl group, a C_{1-4}haloalkyl group (e.g., $-CF_3$, $-CH_2CF_3$), or a C_{5-20}aryl group;

wherein the C_{5-20}aryl group, the C_{5-20}heteroaryl group, and aryl moiety of the C_{7-9}aralkyl group may optionally be substituted on carbon with from 1 to 4 substituents selected from -COOH, -OH, $-NH_2$, $-CH_2NH_2$, $-(CH_2)_{1-4}COOH$, tetrazol-5-yl, and $-SO_3H$;

and wherein the C_{3-6}cycloalkyl group may optionally carry a methyl group;

R^{11} represents -H, a C_{1-6}alkyl group, or a C_{3-6}cycloalkyl group;

R^{12} is one of:

(a) a C_{3-7}cycloalkyl group;

(b) a C_{1-6}alkyl group, optionally substituted with one or more of: a phenyl group; a phenyl group with from 1 to 5 substituents selected from halogen, $-NO_2$, $-CF_3$, C_{1-4}alkyl, C_{1-4}alkoxy, $-NH_2$, $-NHCOCH_3$, $-CONH_2$, $-OCH_2COOH$, $-NH(C_{1-4}alkyl)$, $-N(C_{1-4}alkyl)_2$,

$-NHCOOC_{1-4}$alkyl, -OH, -COOH, -CN and $-COOC_{1-4}$alkyl; a C_{1-4}alkyl group; a C_{1-4}haloalkyl group; or a halogen; and,

(c) a C_{1-6}perfluoroalkyl group;

M represents -S-, -SO-, or $-SO_2-$; and,

Het represents a 5 or 6 membered heterocyclic aromatic ring linked to M via a carbon atom of the aromatic ring, said aromatic ring containing 1, 2, 3 or 4 heteroatoms selected from the group consisting of O, N and S said aromatic ring optionally being substituted on carbon atoms of the ring with 1, 2, 3 or 4 substituents selected from the group consisting of -OH, -SH, -CN, $-CF_3$, NH_2 and halogen.

2. A compound according to claim 1, wherein:
R^1 and R^2 are independently -I, -Br, or -Cl.

3. A compound according to claim 1, wherein:
R^1 and R^2 are both -I.

4. A compound according to any one of claims 1 to 3, wherein:
R^{1a}, R^{1b}, R^{2a}, R^{2b} are each independently -H or $-CH_3$.

5. A compound according to any one of claims 1 to 3, wherein:
R^{1a}, R^{1b}, R^{2a}, R^{2b} are all -H.

6. A compound according to any one of claims 1 to 5, wherein:
R^3 and R^4 are $-CF_3$ and -H, respectively.

7. A compound according to any one of claims 1 to 5, wherein:
R^3 and R^4 are both -F.

8. A compound according to any one of claims 1 to 5, wherein:
R^3 and R^4 are $-CF_3$ and -H, respectively; and,
R^5 is -H.

9. A compound according to any one of claims 1 to 5, wherein:
R^3 and R^4 are both -F; and,
R^5 is -F.

10. A compound according to any one of claims 1 to 5, wherein:
R^3 and R^4 are both -F; and,
R^5 is -H.

11. A compound according to any one of claims 1 to 10, wherein:
Z is $-CH_2-T-C(=O)OH$ or $-CH_2-T-C(=O)OR^8$; and,
T is $-CH_2-$.

12. A compound according to any one of claims 1 to 11, wherein:
R^8 is -H, $-C(CH_3)_3$, or $-CH_2-CH=CH_2$.

13. A compound selected from:
{3,5-difluoro-4-[bis(2-iodoethyl)amino]benzoyl}-L-glutamic acid; and,
the di-*tert*-butyl ester thereof.

14. A compound selected from:
3,5-difluoro-4-[bis(2-chloroethyl)amino]benzoyl}-L-glutamic acid; and,
the di-*tert*-butyl ester thereof.

15. A compound selected from:
{3,5-difluoro-4-[bis(2-bromoethyl)amino]benzoyl}-L-glutamic acid; and,
the di-*tert*-butyl ester thereof.

16. A compound selected from:
{2,3,5-trifluoro-4-[bis(2-chloroethyl)amino]benzoyl}-L-glutamic acid; and,
the di-*tert*-butyl ester thereof.

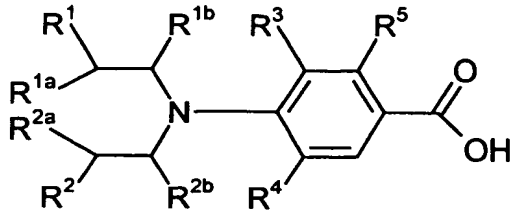
17. A compound selected from:
{2,3,5-trifluoro-4-[bis(2-bromoethyl)amino]benzoyl}-L-glutamic acid; and,
the di-*tert*-butyl ester thereof.

18. A compound selected from:
{2,3,5-trifluoro-4-[bis(2-iodoethyl)amino]benzoyl}-L-glutamic acid; and,
the di-*tert*-butyl ester thereof.

19. A compound selected from:
{3,5-difluoro-4-[bis(2-bromopropyl)amino]benzoyl}-L-glutamic acid; and,
the di-*tert*-butyl ester thereof.

20. A compound selected from:
{3-trifluoromethyl-4-[bis(2-bromoethyl)amino]benzoyl}-L-glutamic acid; and,
the di-*tert*-butyl ester thereof.

21. A compound of Formula II:



wherein:

R^1 is -Cl, -Br, -I, $-OSO_2CH_3$, or $-OSO_2Ph$;

R^2 is -Cl, -Br, -I, $-OSO_2CH_3$, or $-OSO_2Ph$;

wherein Ph denotes a phenyl group which is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from a C_{1-4} alkyl group, -F, -Cl, -Br, -I, -CN, or $-NO_2$;

R^{1a} is -H, a C_{1-4}alkyl group, or a C_{1-4}haloalkyl group ;

R^{2a} is -H, a C_{1-4}alkyl group, or a C_{1-4}haloalkyl group ;

R^{1b} is -H, a C_{1-4}alkyl group, or a C_{1-4}haloalkyl group ;

R^{2b} is -H, a C_{1-4}alkyl group, or a C_{1-4}haloalkyl group ;

R^3 is -F, -Cl, -Br, -I, $-OCHF_2$, -C≡CH, $-OCF_3$, $-CH_3$, $-CF_3$, $-SF_5$, $-SCF_3$, or $-CF_2CF_3$;

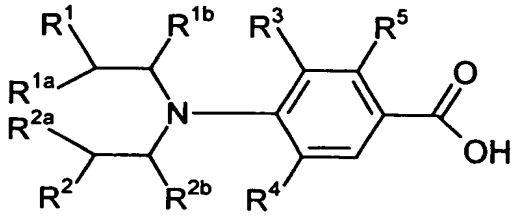
R^4 is -H, -F, -Cl, -Br, -I, $-OCHF_2$, -C≡CH, $-OCF_3$, $-CH_3$, $-CF_3$, $-SF_5$, $-SCF_3$, or $-CF_2CF_3$;

R^5 is -H or -F;

with the proviso that if R^4 is -H, then R^3 is not -F; and,

with the proviso that if R^1 is -Cl, R^2 is -Cl, R^{1a} is -H, R^{2a} is -H, R^{1b} is -H, R^{2b} is -H, R^4 is -H, and R^5 is -H, then R^3 is not $-CH_3$.

22. A compound of Formula II:



wherein:

R^1 is -Cl, -Br, -I, $-OSO_2CH_3$, or $-OSO_2Ph$;

R^2 is -Cl, -Br, -I, $-OSO_2CH_3$, or $-OSO_2Ph$;

wherein Ph denotes a phenyl group which is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from a C_{1-4} alkyl group, -F, -Cl, -Br, -I, -CN, or $-NO_2$;

R^{1a} is -H, a C_{1-4}alkyl group, or a C_{1-4}haloalkyl group ;

R^{2a} is -H, a C_{1-4}alkyl group, or a C_{1-4}haloalkyl group ;

R^{1b} is -H, a C_{1-4}alkyl group, or a C_{1-4}haloalkyl group ;

R^{2b} is -H, a C_{1-4}alkyl group, or a C_{1-4}haloalkyl group ;

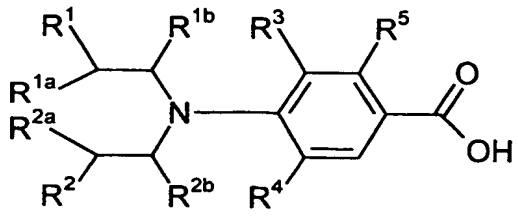
R^3 is -F, -Cl, -Br, -I, $-OCHF_2$, $-C\equiv CH$, $-OCF_3$, $-CF_3$, $-SF_5$, $-SCF_3$, or $-CF_2CF_3$;

R^4 is -H, -F, -Cl, -Br, -I, $-OCHF_2$, $-C\equiv CH$, $-OCF_3$, $-CF_3$, $-SF_5$, $-SCF_3$, or $-CF_2CF_3$;

R^5 is -H or -F;

with the proviso that if R^4 is -H, then R^3 is not -F.

23. A compound of Formula II:



wherein:

R^1 is -Cl, -Br, -I, $-OSO_2CH_3$, or $-OSO_2Ph$;

R^2 is -Cl, -Br, -I, $-OSO_2CH_3$, or $-OSO_2Ph$;

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wherein Ph denotes a phenyl group which is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from a C_{1-4} alkyl group, -F, -Cl, -Br, -I, -CN, or $-NO_2$;
R^{1a} is -H, a C_{1-4}alkyl group, or a C_{1-4}haloalkyl group ;
R^{2a} is -H, a C_{1-4}alkyl group, or a C_{1-4}haloalkyl group ;
R^{1b} is -H, a C_{1-4}alkyl group, or a C_{1-4}haloalkyl group ;
R^{2b} is -H, a C_{1-4}alkyl group, or a C_{1-4}haloalkyl group ;
R^3 and R^4 are $-CF_3$ and -H, respectively,
or R^3 and R^4 are both -F;
R^5 is -H or -F.

24. A compound according to any one of claims 21 to 23, wherein:
R^1 and R^2 are independently -I, -Br, or -Cl.

25. A compound according to any one of claims 21 to 23, wherein:
R^1 and R^2 are both -I.

26. A compound according to any one of claims 21 to 25, wherein:
R^{1a}, R^{1b}, R^{2a}, R^{2b} are each independently -H or $-CH_3$.

27. A compound according to any one of claims 21 to 25, wherein:
R^{1a}, R^{1b}, R^{2a}, R^{2b} are all -H.

28. A compound according to any one of claims 21 to 27, wherein:
R^3 and R^4 are $-CF_3$ and -H, respectively.

29. A compound according to any one of claims 21 to 27, wherein:
R^3 and R^4 are both -F.

30. A compound according to any one of claims 21 to 27, wherein:
R^3 and R^4 are $-CF_3$ and -H, respectively; and,
R^5 is -H.

31. A compound according to any one of claims 21 to 27, wherein:
R^3 and R^4 are both -F; and,
R^5 is -F.

32. A compound according to any one of claims 21 to 27, wherein:
R^3 and R^4 are both -F; and,
R^5 is -H.

33. 3,5-difluoro-4-[bis(2-iodoethyl)amino]benzoic acid.

34. 3,5-difluoro-4-[bis(2-chloroethyl)amino]benzoic acid.

35. 3,5-difluoro-4-[bis(2-bromoethyl)amino]benzoic acid.

36. 2,3,5-trifluoro-4-[bis(2-chloroethyl)amino]benzoic acid.

37. 2,3,5-trifluoro-4-[bis(2-bromoethyl)amino]benzoic acid.

38. 2,3,5-trifluoro-4-[bis(2-iodoethyl)amino]benzoic acid.

39. 3,5-difluoro-4-[bis(2-bromopropyl)amino]benzoic acid.

40. 3-trifluoromethyl-4-[bis(2-bromoethyl)amino]benzoic acid.

41. A two-component system comprising:

(i) a first component capable of delivering a carboxypeptidase enzyme to the interior or exterior of a target cell or a vector encoding said enzyme to the interior of said cell such that said vector expresses said enzyme in said cell, and

(ii) a prodrug of according to any one of claims 1 to 20 capable of being converted by said enzyme into a drug according to any one of claims 21 to 40.

42. A kit comprising:

(a) a compound according to any one of claims 1 to 20; and,

(b) one of:

(i) an immunoglobulin/enzyme fusion protein or conjugate in which the immunoglobulin is specific for a cellular antigen and the enzyme is a carboxypeptidase enzyme;

(ii) a ligand/enzyme conjugate or fusion protein, the ligand being specific for a cellular antigen and the enzyme is a carboxypeptidase enzyme;

(iii) a vector which encodes a carboxypeptidase enzyme which can be expressed in a cell.

43. A composition comprising a compound according to any one of claims 1 to 40, and a pharmaceutically acceptable carrier or diluent.

44. A compound according to any one of claims 1 to 40 for use in a method of treatment of the human or animal body.

45. A compound according to any one of claims 1 to 40 for use in a method of treatment of cancer of the human or animal body.

46. Use of a compound according to any one of claims 1 to 40 for the manufacture of a medicament for use in the treatment of cancer.

47. A method for the treatment of cancer comprising administering to a subject suffering from cancer a therapeutically-effective amount of a compound according to any one of claims 1 to 40.